LET’S START WITH A CASE

Case Presentation

- 22 yo U.S. Army Active Duty male deployed to Afghanistan west of Kandahar presents with fever (102.5^{o} F), headache, fatigue, chills, abdominal pain with non-bloody diarrhea (SEP 8, 2009)
  - Symptoms progressing over the previous 4 days
- Initially told he had a “gastroenteritis” at local clinic
  - Treated with Cipro and immodium
  - 48 hour quarters
- Returned the following day (SEP 9):
  - Symptoms worsening, now with nausea/vomiting and lethargy
  - Told he may have a “viral syndrome”
  - Referred to Kandahar for observation

Case Presentation

- Progressively worsened over the next several hours
  - Lethargy lead to somnolence
  - Bloody diarrhea and bleeding gums
  - Shortness of breath → intubated
  - Anemic, low platelets, developing organ failure

- Evacuated to LRMC with presumed diagnosis of pneumonia with septic shock (antibiotics started)

Case Presentation

- Upon arrival at the Landstuhl Regional Medical Center, he is found to be bleeding EVERYWHERE
  - Petechiae everywhere
  - Large ecchymotic lesions at IV sites
  - Extremely sick
- He requires emergent bronchoscopy for bleeding
- The ICU staff raises the concern for viral hemorrhagic fever


a


b


c


d

Case Presentation

- Co-located with Afghan army
- Potential exposures
  - Numerous outdoor activities to include sleeping outside
  - Recent tick exposures
    - Patient and battle buddy both with recent bites within a week of illness onset
    - This was a common occurrence (bragging rights)
  - Exposure to goat blood and undercooked goat meat


AFGHANISTAN
UZBEKISTAN
TAJIKISTAN
CHINA
TURKMENISTAN
Badakhshan
Mazar-
e-Sharif
Kunduz
Tashkurghan
HINDU
KUSH
Pul-e Khumri
Nuristan
Bamiyan
Chaghcheran
Kabul
Jalalabad
Herat
Minaret of Jam
Farah River
Ghazni
Gardez
Helmand
Valley
Farah
IRAN
Girishk
PAKISTAN
Kandahar
Lashkar Gah
Zaranj
Helmand River
INDIA
Dasht-e Margo
0
300 km
0
180 miles

Case Presentation

- Blood sent to the Bernard Nocht Institute (BNI) in Hamburg within hours of admission
- Blood run overnight
  - SEP 10: PCR and IGM **POSITIVE** for CCHF
  - Infectious diseases consulted just prior to test results
- Within ~12 hours of diagnosis, treatment with oral ribavirin thru feeding tube
  - Dose given to match the standard IV dose
- Emergency IND approval for IV ribavirin from the FDA
- IV ribavirin started 12 hours after oral treatment (48 hours of hospitalization)

Case Presentation

- Renal and hepatic dialysis started
- Patient appeared to be improving

- However:
- SEP 14
  - Patient had a asystolic/PEA arrest
  - Declared brain dead
    - At time of death, viral load had declined and antibodies present
    - Cerebral edema on CT

Viral Hemorrhagic Fevers

Kris Paolino, MD
Chief, Clinical Trials Center
Walter Reed Army Institute of Research
July 2014

Thanks to:

COL Mark Kortepeter, MD, MPH

Will Cover Some Steps to Avoid….

The “Slammer”


BSL-4
CONTAINMENT SUITE
MAGNEHELIC
MAJ Muckerman OIC
SECURE AREA
AUTHORIZED

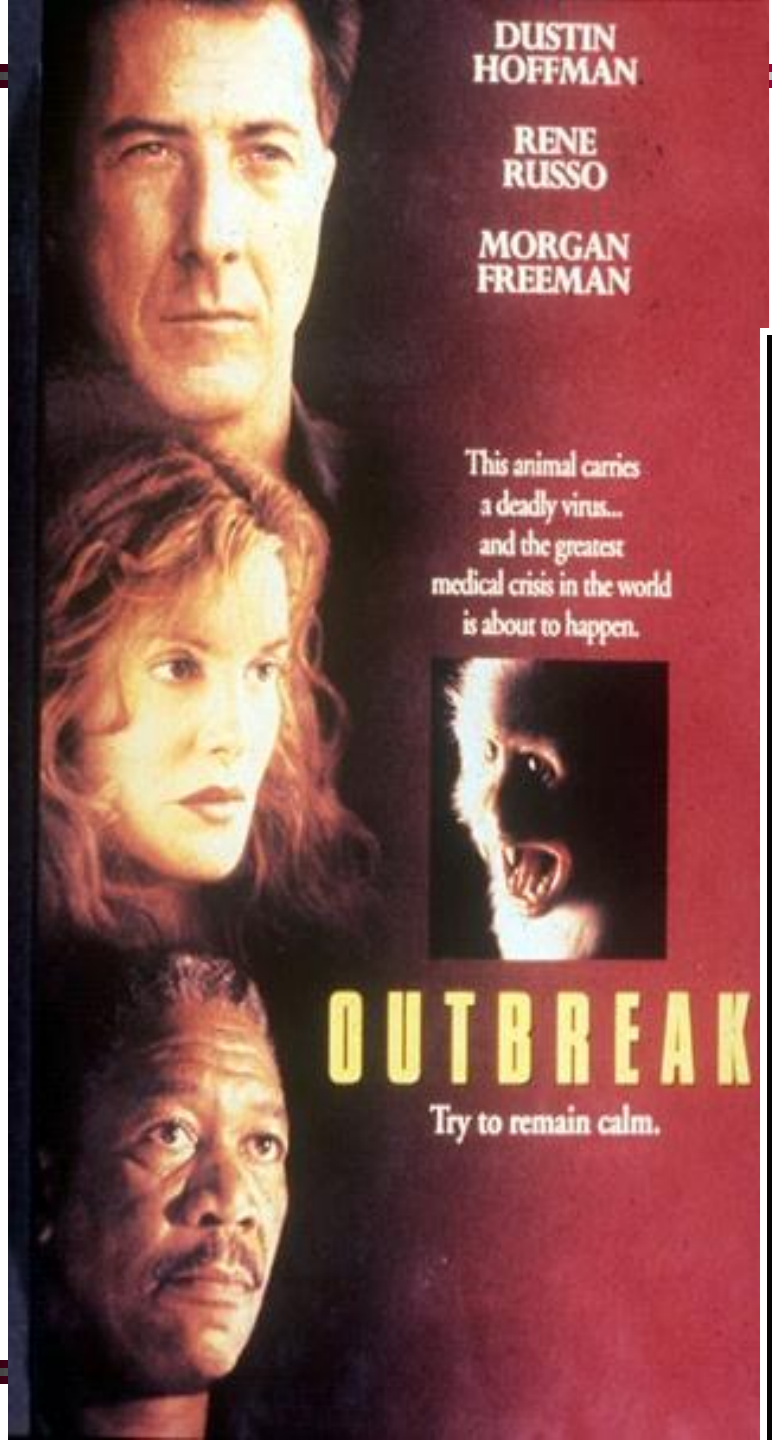
1995 Kikwit Zaire ZEBOV Outbreak

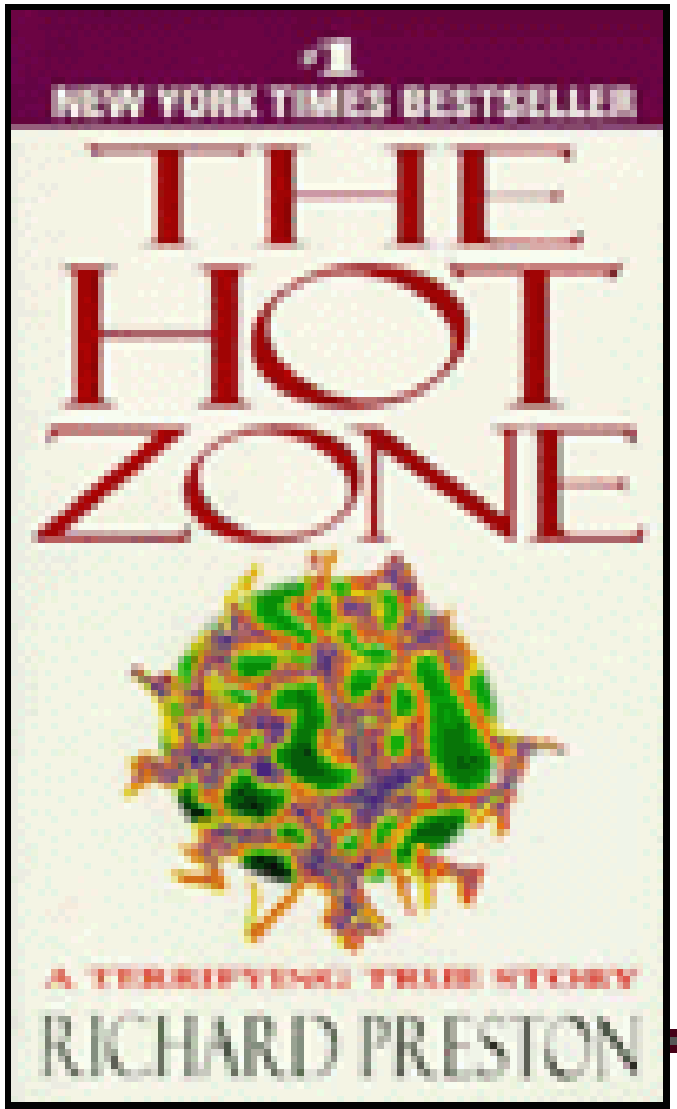
Courtesy of Don Noah


EXIT
KORTEPETER
WHITE

Outline

- VHFs – Overview of Syndrome
- Selected Pathogens:
  - Ebola
  - Crimean-Congo Hemorrhagic Fever
  - Lassa Fever
  - Hantaviruses
- Emerging Threats


DUSTIN HOFFMAN
RENE RUSSO
MORGAN FREEMAN
This animal carries a deadly virus... and the greatest medical crisis in the world is about to happen.
OUTBREAK
Try to remain calm.


#1
NEW YORK TIMES BESTSELLER
THE HOT ZONE
A TERRIFYING TRUE STORY
RICHARD PRESTON

Potential of VHF's for Weaponization

- PRO
  - **Many demonstrated as infectious by aerosol transmission**
    - **Exception is Dengue**
  - **Potentially high morbidity and mortality**
  - **Replicate well in cell culture**
    - **Exception are viruses in *Bunyaviridae* (e.g. CCHF)**
  - **Capability to overwhelm medical resources**
  - **Frightening effects of illness / terror value**
- CON
  - **Lack of treatment or vaccine to protect user's own "troops"**
    - **May not be deterrent for some countries / non-state actors**
  - **Possible entry into local vector / reservoir population**
  - **Stabilizers must be used to enhance viability**

Other Military Relevance: History of Weaponization

- Yellow fever and RVF were weaponized by the U.S. during their offensive program
- Former Soviet Union produced large quantities of Ebola, Marburg, Lassa, Junin, and Machupo
- Yellow fever may have been weaponized by North Koreans
- **The Aum Shinrikyo cult unsuccessfully tried to obtain Ebola virus to create biological weapons**
- Several studies have demonstrated ability to aerosolize Ebola, Marburg, Lassa, and some of the New World arenaviruses

United State Army Medical Research Institute of Infectious Diseases (USAMRIID)

Definition

- **Viral hemorrhagic fever (VHF):**
  - **Fever**
  - **Malaise**
  - **Myalgia prostration**
  - **Bleeding diathesis**
  - **Severe multi-organ failure**
  - **Enveloped, single-stranded, *RNA viruses***

•Hemorrhagic fever virus (HFV) is a term used to generically identify those agents that cause VHF

Overview of VHFs

- **Clinical Presentation**
  - Variety of presentations
  - **Prodrome**
    - High fever, Headache, Malaise, Arthralgias, Myalgias
    - Nausea, Abdominal pain, Non-bloody diarrhea
  - **Early signs**
    - Fever, Tachycardia, Tachypnea, Conjunctivitis, Pharyngitis
    - Flushing, Skin Rash
  - **Late**
    - ↓ BP, Hemorrhagic diathesis, Petechiae, Mucous membrane
    - Conj. hemorrhage, Hematuria, Hematemesis, Melena
  - **Severe Manifestations**
    - DIC, Circulatory Shock, CNS dysfunction, Death
    - Mortality rates can be as high as 90%+

Overview of VHFs

DISEASE	Hemorrhage	Thrombocyto-penia	Leucocyte count	Rash	Icterus	Renal Disease	Pulmonary Disease	Tremor, Dysarthria	Encephalo-pathy	Deafness	Eye Lesions
ARENAVIRIDAE											
South American HF	+++	+++	⇩⇩⇩	0	0	0	+	+++	++	0	0
Lassa fever	+/S	+	0	++	0	0	+	+	+/S	++	0
BUNYAVIRIDAE											
Rift Valley fever	+++	+++		0	++	+		0	E	0	Retina
Crimean Congo HF	+++	+++	⇩⇩/⇧	0	++	0	+	0	+	0	0
HFRS	+++	+++	⇧⇧⇧	0	0	+++	+	0	+	0	0
HPS	+	++	⇧⇧	0	0	+	+++	0	+	0	0
FILOVIRIDAE											
Marburg and Ebola HF	++	+++		+++	++	0	+	0	++	+	Uveitis Retina?
FLAVIVIRIDAE											
Yellow fever	+++	++	0/⇩⇩	0	+++	++	+	0	++	0	0
DHF/DSS	++	+++	⇧⇧	+++	+	0	+	0	+	0	0
KFD/OHF	++	++	⇩⇩	0	0	0	++	0	E	0	Retina

Courtesy of Drs. Zaki & Peters

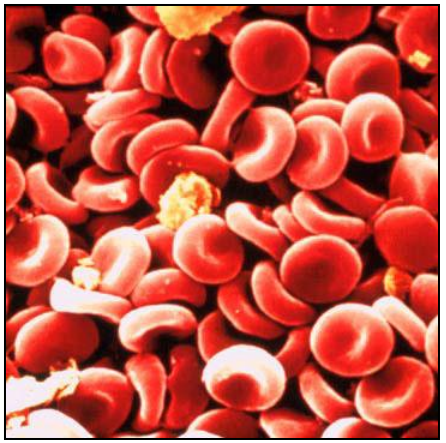
\+ occasional or mild
++ commonly seen, may be severe
+++ characteristic and usually marked

S characteristic, seen in severe cases

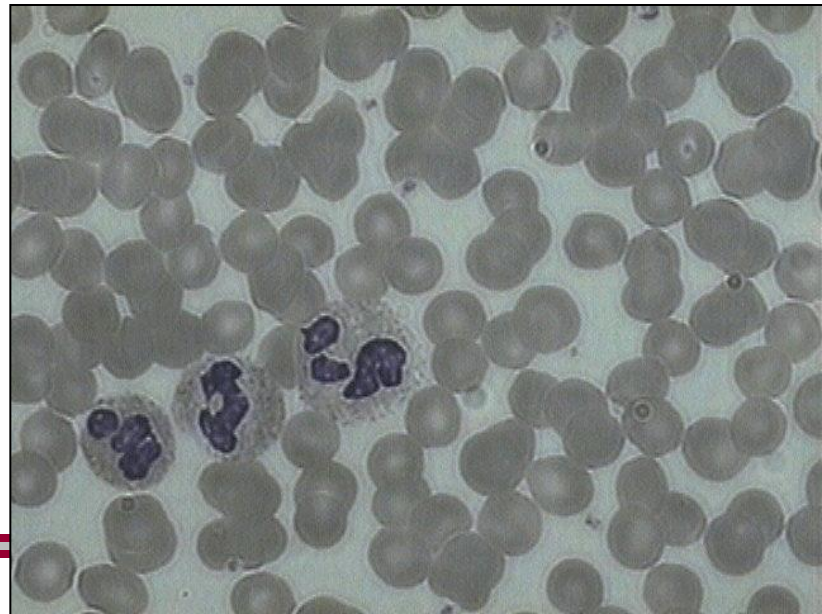
⇧ occasionally or mildly increased
⇧⇧ commonly increased, may be marked
⇧⇧⇧ characteristically increased and usually marked

E Develop true encephalitis but either after HF (KFD, Omsk) or in other patients (RVF)

Overview of VHFs



- **Lab Abnormalities**
  - Leukopenia
    - Lassa with leukocytosis (WBC inc.)
  - Anemia
  - Hemoconcentration
  - Thrombocytopenia
  - Elevated liver enzymes
  - May have renal dysfunction
  - Coagulation abnormalities



Overview of VHFs

- **Lab Abnormalities**
  - Coagulation abnormalities
    - Prolonged bleeding time
    - Prothrombin time
    - Activated PTT
    - ↑ fibrin degradation (i.e. increased D-dimer)
    - ↓ fibrinogen
  - Urinalysis
    - Proteinuria
    - Hematuria
    - Oliguria
    - Azotemia

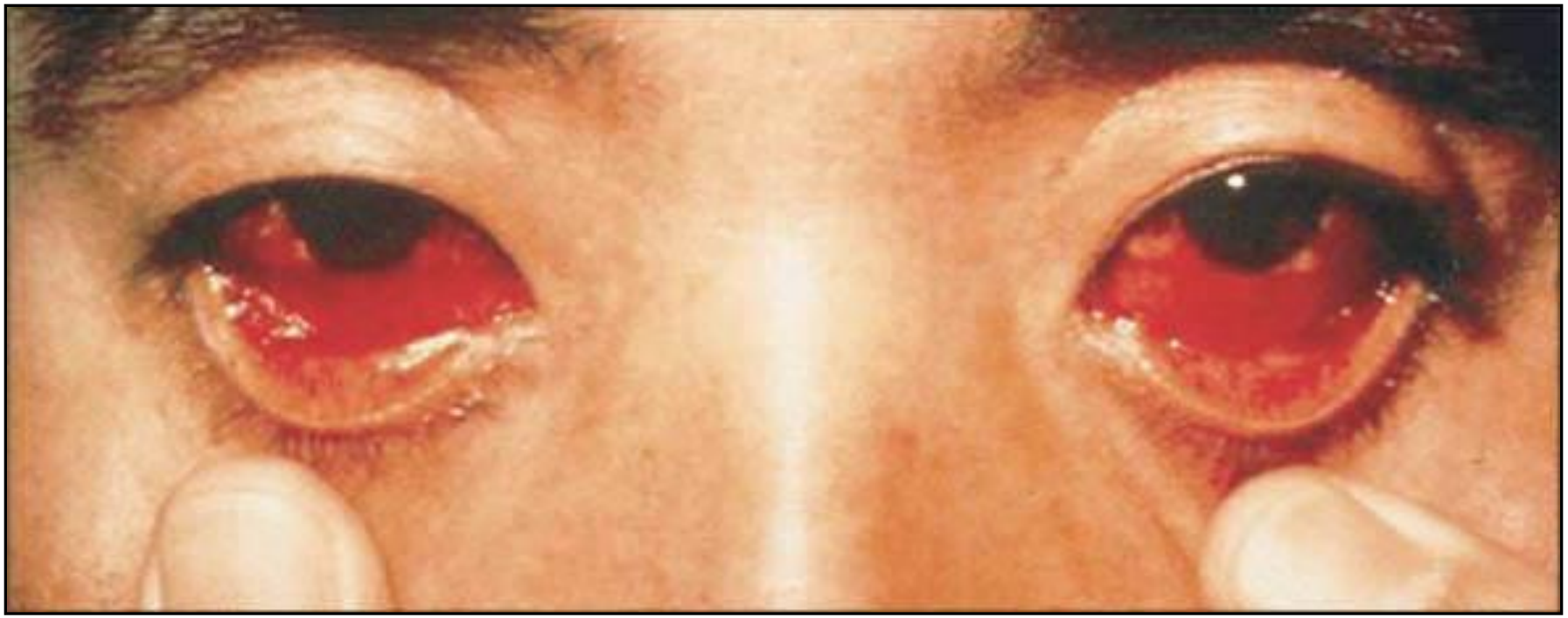
Overview of VHFs

- **Lab Abnormalities**
  - **These are not hard and fast rules.**
  - **There will be overlap with many of these infections**

Argentine Hemorrhagic Fever (Junin virus – New World Arenavirus)

Gingival hemorrhage

Bolivian Hemorrhagic Fever (Machupo virus – New World Arenavirus)



Conjunctival injection & subconjunctival hemorrhage

Ref: Current Science/Current Medicine (Peters CJ, Zaki SR, Rollin PE). Viral hemorrhagic fevers. In: Fekety R, vol ed. Atlas of Infectious Diseases, p10.1-10.26, Volume VIII, 1997.

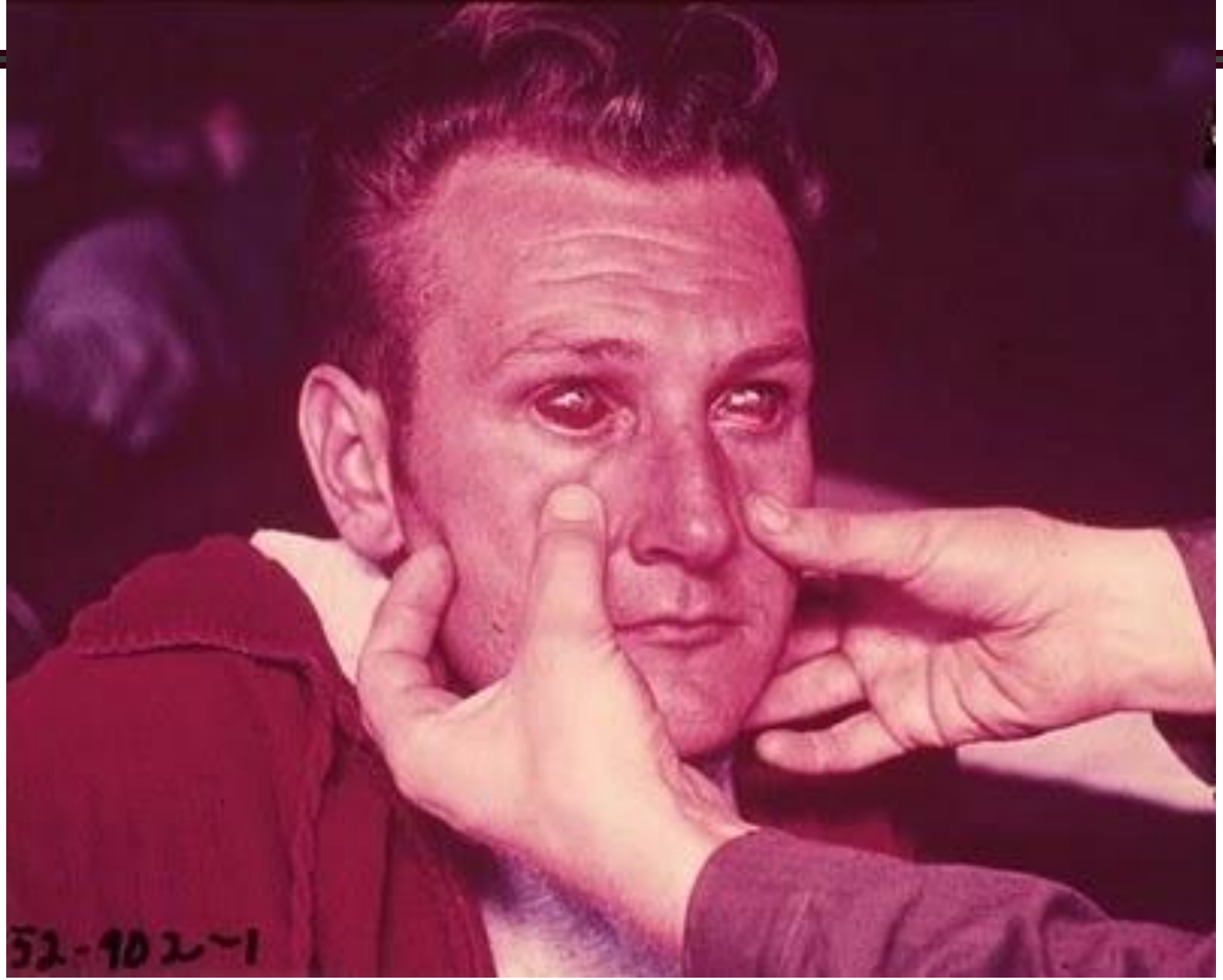
CCHF

Left arm. Ecchymosis, diffuse, severe.
(1 week after clinical onset)

Photo credit: Robert Swaneopoel, PhD, DTVM, MRCVS, National Institute of Virology, Sandringham, South Africa.

DENGUE


CCHF



KOREAN HEMORRHAGIC FEVER (HANTAAN)

DENGUE

BOLIVIAN HEMORRHAGIC FEVER (MACHUPO)

KOREAN HEMORRHAGIC FEVER (HANTAAN)


CCHF

CCHF

Marburg Infection Human

Maculopapular rash

Photo credit: Martini GA, Knauff HG, Schmidt HA, et. al. *Ger Med Mon*. 1968:13:457-470.

Overview of VHFs

- **General Summary of What is Known…**
  - Pathogens
  - Geographic distribution
  - Animal hosts and vectors
  - Nosocomial and occupational risks
  - Estimated incubation periods

Overview of Etiologic Agents of VHFs

Family	Genus	Species
Filoviridae	*Ebolavirus*	Zaire, Sudan, Ivory Coast, Reston, Bundibugyo
	Marburgvirus	Lake Victoria marburgvirus
Arenaviridae	*Arenavirus*	Lassa, Lujo (“Old World”) Junin, Machupo, Guanarito, Sabia, (“New World”)
Bunyaviridae	*Nairovirus*	Crimean-Congo hemorrhagic fever
	Phlebovirus	Rift Valley fever
	Hantavirus	Hantaan, Seoul, Puumala, Dobrava, Sin Nombre
Flaviviridae	*Flavivirus*	Omsk HF Kyasanur forest disease (including Alkhurma) Dengue Yellow fever

Disease (Virus)	Distribution	Host/Vector	Other risks	Incubation	CFR
Ebola	Africa, Philippines (ER)	Bats/Pigs?	Nosocomial	2-21	25 - 88% (~67%)
Marburg	Africa	Bats?	Nosocomial	5-10	82%
Lassa (and Lujo)	Africa (Western)	Rodent	Nococomial	5-16	15-20%
Junin	Argentina	Rodent	Nococomial	7-14	10-30%
Machupo	Bolivia	Rodent	Nococomial	9-15	5-30%
Guanarito	Venezuela	Rodent	Nococomial	7-14	23%
Sabia	Brazil	Rodent	Nococomial	7-14	1 of 3
Crimean-Congo	Europe, Asia, Africa	Tick, herding animals, birds?	Nosocomial, slaughterhouse	3-12	3 - 70% (~20-30%)
Rift Valley Fever	Africa	Mosquito	slaughterhouse	2-6	1 - 50%
Hantaviruses	Worldwide	Rodent	Nosocomial (Andes virus)	9-35	1-15% (~50% HPS)
Omsk	Soviet Union	Tick		2-9	0.3-5%
Kyasanur	India	Tick		2-9	3-5%
Alkhumra	Middle East	Tick (Camels?)	Butchers	2-9	~30%
Yellow Fever	Africa, Americas	Mosquito		3-6	20-50%

The "Deadly" VHFs

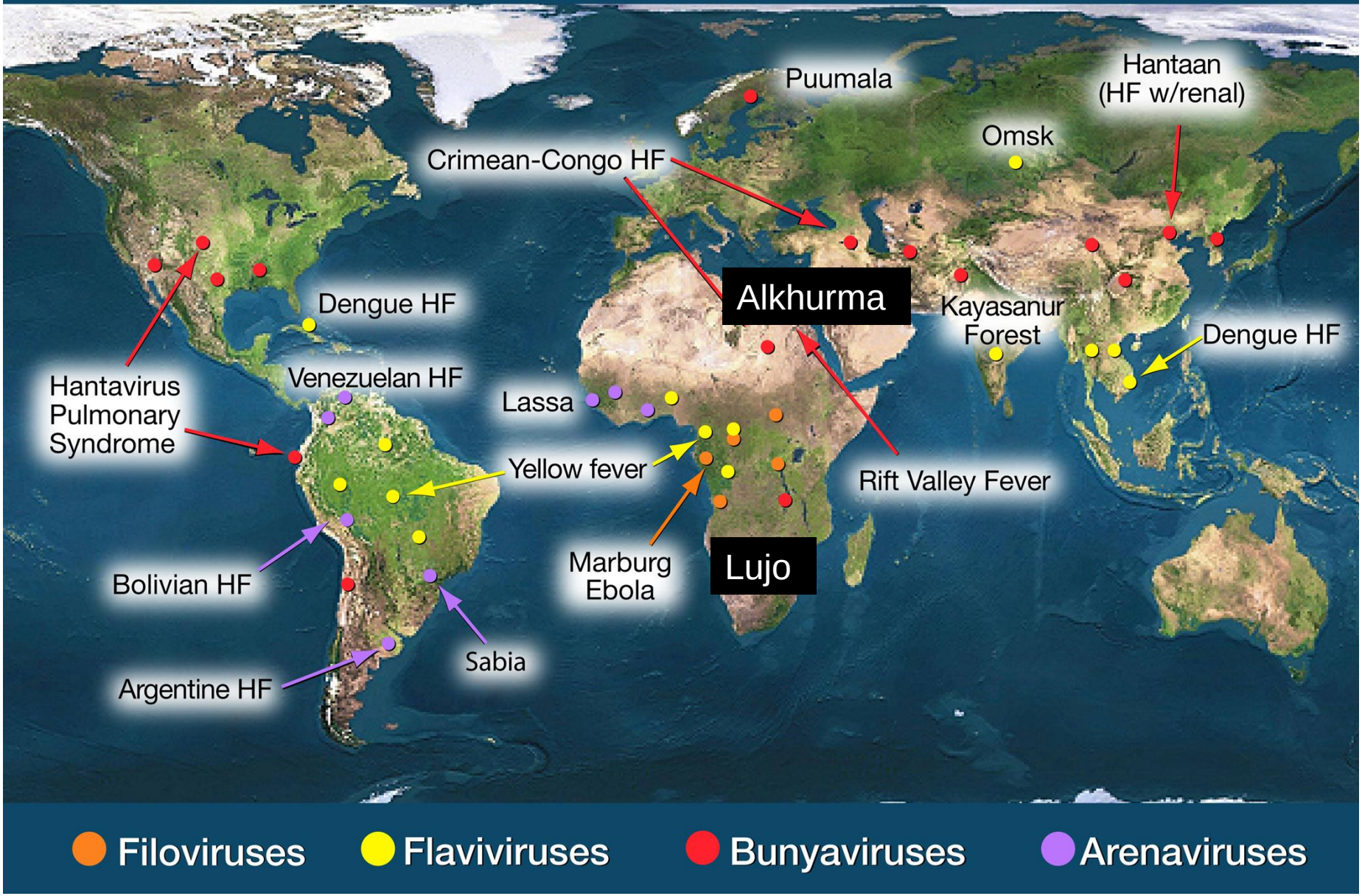
VIRUS	Mortality Rate
Ebola Zaire	75-90%
Marburg	25-90%
Lassa	15-20% of hospitalized
CCHF	3-70% (typically 20-30%)
Rift Valley fever	50% of patients with hemorrhagic form

Overview of VHFs

- **Geography of VHF**

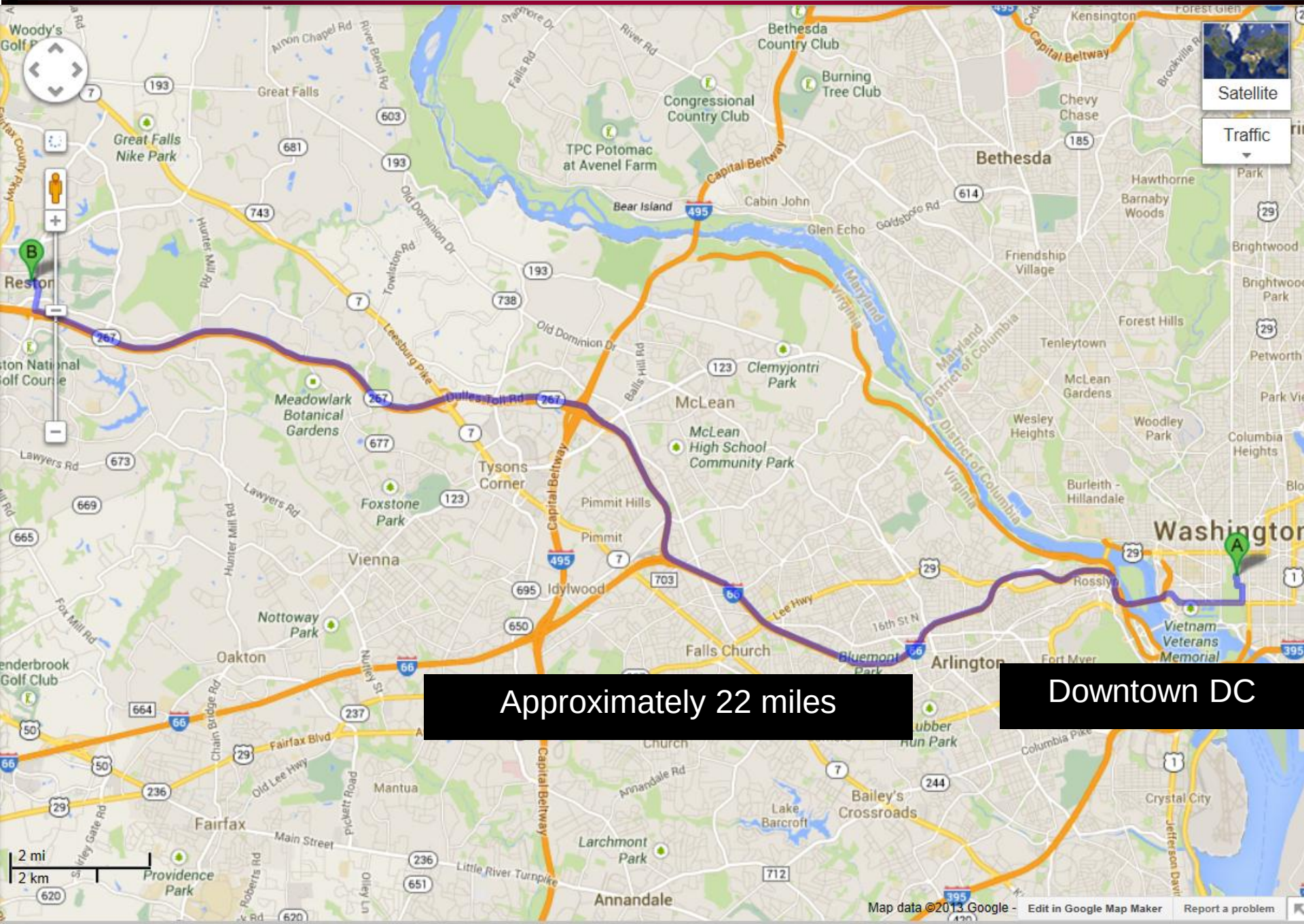

MORE AMERICA!!
santa!!
uninhabited
AMERICA!!!!1
WE'RE#1!!!!!
MORE AMERICA!!
don't drink the water
cruise ships go here
coffee comes from here i think
COMMUNISTS
friend
evil-doers!!
bombs go here
tvs and cameras
they make our stuff
more evil-doers
call centers
zoo animals come from here
kangaroos
cold!

Viral Hemorrhagic Fever



Courtesy of Mike Bray, NIAID

Ebola Reston



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MMWR Weekly

December 18, 2009 / 58(49);1377-1381

Imported Case of Marburg Hemorrhagic Fever --- Colorado, 2008

Marburg hemorrhagic fever (MHF) is a rare, viral hemorrhagic fever (VHF); the causative agent is an RNA virus in the family *Filoviridae*, and growing evidence demonstrates that fruit bats are the natural reservoir of Marburg virus (MARV) (*1,2*). On January 9, 2008, an infectious disease physician notified the Colorado Department of Public Health and Environment (CDPHE) of a case of unexplained febrile illness requiring hospitalization in a woman who had returned from travel in Uganda. Testing of early convalescent serum demonstrated no evidence of infection with agents that cause tropical febrile illnesses, including VHF. Six months later, in July 2008, the patient requested repeat testing after she learned of the death from MHF of a Dutch tourist who had visited the same bat-roosting cave as the patient, the Python Cave in Queen Elizabeth National Park, Uganda (*3*). The convalescent serologic testing revealed evidence of prior infection with MARV, and MARV RNA was detected in the archived early convalescent serum. A public health investigation did not identify illness consistent with secondary MHF transmission among her contacts, and no serologic evidence of infection was detected among the six tested of her eight tour companions. The patient might have acquired MARV infection through exposure to bat secretions or excretions while visiting the Python Cave. Travelers should be aware of the risk for acquiring MHF in caves or mines inhabited by bats in endemic areas in sub-Saharan Africa. Health-care providers should consider VHF among travelers returning from endemic areas who experience unexplained febrile illness.

Domestically Acquired Seoul Virus Causing Hemorrhagic Fever with Renal Syndrome—Maryland, 2008

Christian Woods,[1] Rakhee Palekar,[2,3] Peter Kim,[1] David Blythe,[2] Olivier de Senarclens,[1] Katherine Feldman,[2] Eileen C. Farnon,[4] Pierre E. Rollin,[4] Cesar G. Albariño,[4] Stuart T. Nichol,[4] and Margo Smith[1]

[1]Washington Hospital Center, Washington, DC; [2]Maryland Department of Health and Mental Hygiene, Baltimore, Maryland; [3]Epidemic Intelligence Service, Office of Workforce and Career Development, and [4]Special Pathogens Branch, Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

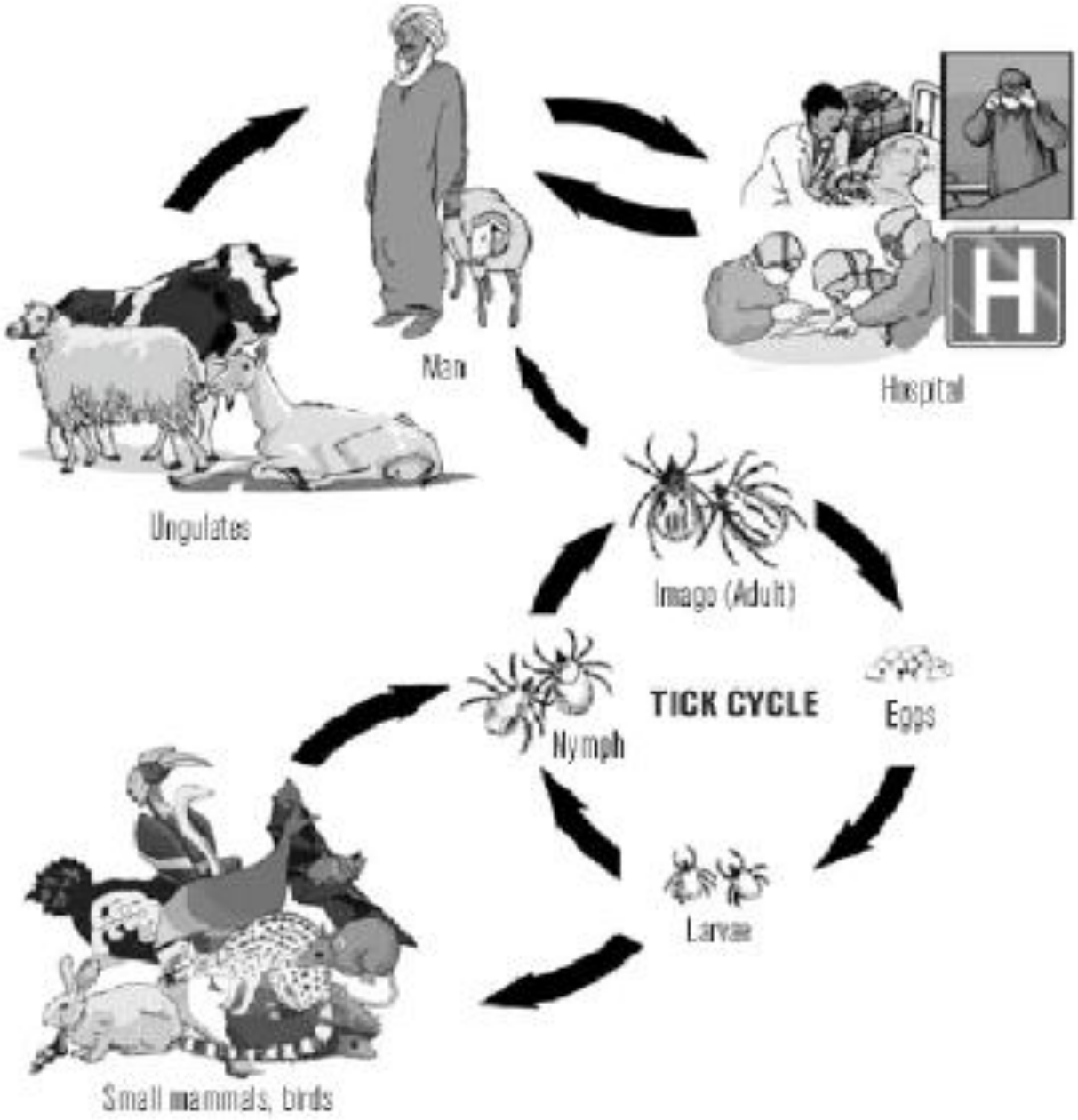
How are VHFs Spread?

1 - Inhaling or ingesting excretions/secretions from rodent hosts (urine, feces)

2 - Bite of an infected arthropod (tick, mosquito)

3 - Nosocomial/lab transmission – contact with human or animal blood/body fluids/tissue

4 - Artificially generated aerosols (biowarfare)


Man
Hospital
H
Ungulates
Imago (Adult)
Eggs
TICK CYCLE
Nymph
Larvae
Small mammals, birds

Overview of VHFs

How are VHFs spread?

Airborne?

- In monkeys, possible airborne transmission between cages 3 m
- Lung tissue, along with nares, pharynx, and conjunctiva w/virus
- Monkeys and guinea pigs able to be infected via airborne route

Arch Pathol Lab Med 1996;120: 140-5.
Int J Exp Path 1995;76:227-36.

Lancet 1995;346:1669-71.
Arch Virol 1996(suppl);11:115-134.

Overview of VHFs

How are VHFs spread?

Human to Human?

Only dengue and yellow fever virus have adapted to efficient "human-to-human" transmission (via mosquitoes).

Typical story for nosocomial transmission:

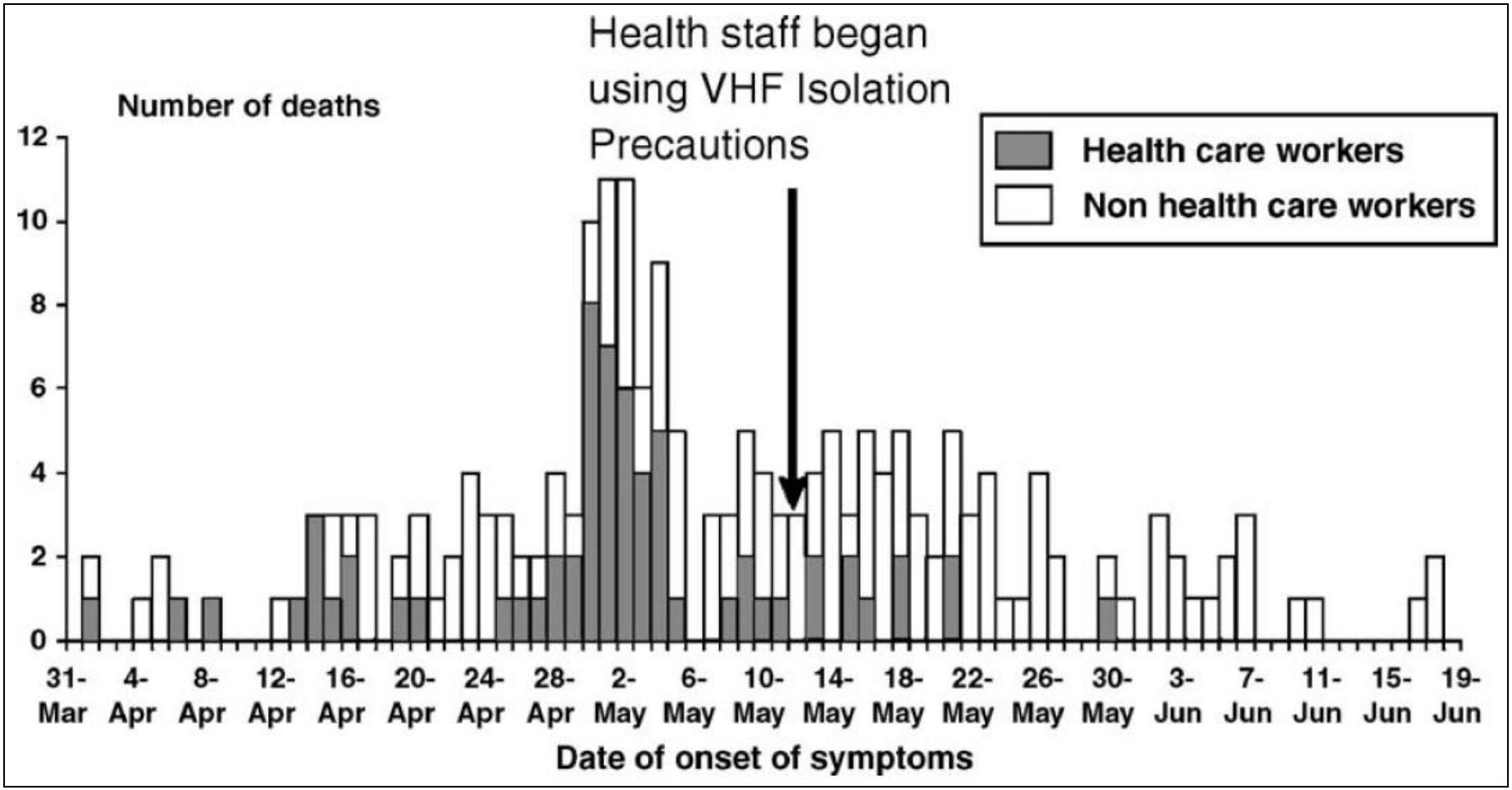
- Patient Zero enters the health care facility
- VHF is not recognized or infection control not followed
- Unrecognized spread from blood/body fluid contact
- Health care personnel among the victims
- Victims carry infection to the community
- Close family members and those doing burial rites infected

No **proven** human to human respiratory transmission

Overview of VHFs

- How are VHFs spread?
  - Usually spread during patient care without appropriate barrier precautions
    - Contact with blood/tissue/body fluids
    - Includes re-use of syringes/needles
  - Epidemiologically, VHFs not readily transmitted person-to-person by airborne route
    - A possibility in only rare circumstances
  - Highest risk in later stages, when having vomiting, diarrhea, shock, hemorrhage
  - Not reported during incubation period (before fever)

MMWR 1995;44(25):475-79.



Number of infected health care workers declined after barrier nursing practices were begun during the Ebola HF outbreak in Kikwit, DRC, 1995.

Critical Care Clinics (2005) 21:765-783.

Overview of VHFs

How are VHFs spread?

Nosocomial

Filoviruses – **Ebola** and **Marburg**

Arenaviruses – **Lassa**, Junin/Machupo (rare)

Bunyaviruses – **CCHF**, Andes virus (a cause of HPS)

Flaviviruses – dengue (rare – from blood splash)

Lassa – most common imported VHF
(if dengue not included)

Transmission of VHFs rarely if ever occur prior to onset of symptoms

Overview of VHFs

Differential Diagnosis

- Malaria
- Typhoid fever (*Salmonella*)
- Rocky Mountain Spotted Fever (*Rickettsia rickettsii*)
- Other rickettsioses
- Leptospirosis
- Meningococci
- Q fever (*Coxiella burnetti*)
- Plague
- Influenza
- Viral meningitis / encephalitis
  - Henipaviruses
- HIV / co-infection
- Hemorrhagic smallpox
- Vasculitis (i.e. autoimmune diseases)
- Thrombotic thrombocytopenic purpura (TTP)
- Hemolytic-uremic syndrome (HUS)
- Hemophagocytic syndrome

Clinical presentation: Fever, hemorrhage/purpura, thrombocytopenia, CNS signs, elevated LFTs, leukopenia, thrombocytopenia, DIC, multisystem / multi-organ failure

Overview of VHFs

This stuff is all great, but in reality you may not have readily available basic labs let alone PCR capabilities

- Diagnosis
  - **<u>High index of suspicion</u> (know what is in your AO)**
  - Lab findings
    - Thrombocytopenia , low WBC, anemia, transaminitis, increased bilirubin, prolonged PT, PTT, increased D-dimer, decreased fibrinogen
  - Virus isolation (Gold Standard, but requires BSL-4 Lab)
  - Electron microscopy
  - Reverse transcription - polymerase chain reaction (RT-PCR)
  - Rapid ELISA techniques (most easily employed)
  - Immunohistochemistry (IHC) & in situ hybridization (ISH) of infected tissues

Distribution of CCHF

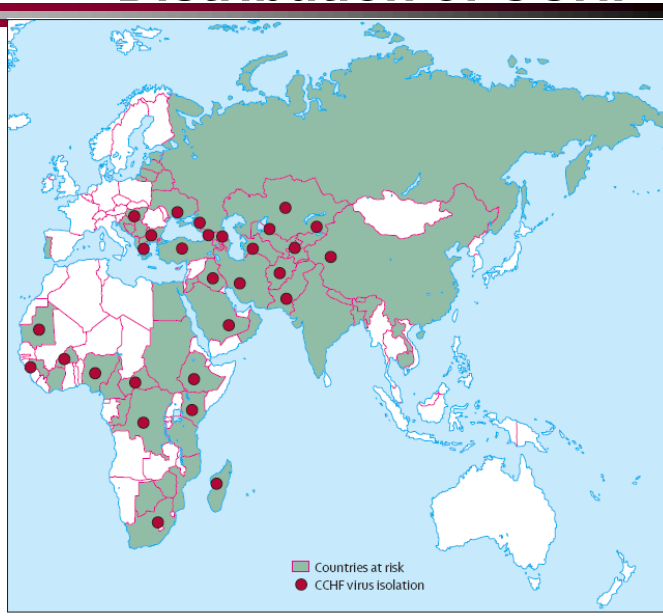
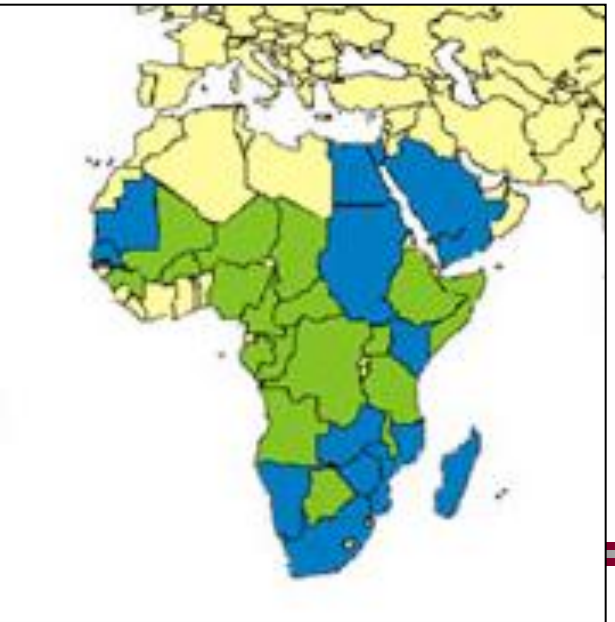


Figure 1: Worldwide distribution of CCHF virus

Distribution of Junin

Distribution of RVF



Antiviral Res 2008:132-39.

Overview of VHFs

- **Treatment**
  - **Supportive Care (the foundation of treatment)**
    - Careful management of fluid and electrolytes
    - Use of colloid
    - Hemodialysis as needed
    - Vasopressors and cardiotonic drugs (some do not respond to fluids)
    - Cautious sedation and analgesia
    - Watch for secondary infections
  - Treatment of Disseminated Intravascular Coagulation (DIC)
    - Coagulation studies and clinical judgment as guide
    - Replacement of coagulation factors / cofactors
    - Platelet transfusions
    - **No aspirin, NSAIDs, anticoagulant therapies, or IM injections**

Overview of VHFs

- **Treatment**
  - Ribavirin
    - Investigational drug, compassionate use
    - **<u>Contraindicated in pregnancy</u>**
    - Arenaviridae (Lassa, Junin, Sabia, Lujo)
    - Bunyaviridae (Hantaan, CCHF) – *not* RVF
    - NO UTILITY FOR FILOVIRUSES OR FLAVIVIRUSES
  - Immune (convalescent) plasma
    - Arenaviridae (Junin, Machupo; ?Lassa)
    - Passive immunoprophylaxis post-exposure?
    - Experimental studies in animals have not proven efficacy against filovirus infection
    - NOT READILY AVAILABLE

Overview of VHFs

- Ribavirin Treatment
  - 33 mg/kg IV single loading dose
  - 16 mg/kg IV q 6 hr for 4 days
  - 8 mg/kg IV q 8hr for 6 days

Risks:
- Upset stomach
- Reversible hemolytic anemia
- Arrhythmias
- Teratogenic

- Ribavirin Post-Exposure Prophylaxis
  - 500 mg PO q 6 hr for 7 days (different regimens)

Note: Parenteral (Rx) and oral Ribavirin (PEP) are **investigational** and available only through human use protocols (ahem….contact USAMRIID or LRMC through ID consult)

Borio L, *et al*. *JAMA* 287(18):2391-2405, 2002
McCormick JB *et. al.* *N Eng J Med* 314(1):20-26, 1986
Jahrling PB *et al. J Infect Dis* 141:580-589, 1980

Overview of VHFs

	Contained Casualty	Mass Casualty
Adults	Same as previous slide	Load 2g po x 1, followed by 1.2g po qd divided in 2 doses (if >75kg pt), or 1g po qd in 2 doses (if pt <75kg) for 10 days
Pregnant	Same as adults	Same as adults
Children	Same as Adults, dosed according to weight	Loading dose 30mg/kg po x1, followed by 15mg/kg qd in 2 divided doses for 10 days

RIBAVIRIN TREATMENT

JAMA 2002;287:2391

Prevention / Control

- YELLOW FEVER
  - Licensed 17D vaccine, highly efficacious
  - Live virus vaccine
  - Reports of vaccine associated deaths
  - Cannot be used in persons with egg allergy

- Junin Candid 1 – ARGENTINE HF
  - Live, attenuated
  - Safe and efficacious
  - Protects monkeys against Bolivian HF
  - **NOT AVAILABLE IN THE UNITED STATES**

Prevention / Control: None Licensed

- Rift Valley Fever
  - Formalin-inactivated
    - safe but requires 3 shots, intermittent booster
    - limited supply
  - Live, attenuated MP-12
    - Phase II testing
- Ebola
  - Adenovirus vectored +/- DNA prime
  - VEE replicons
  - VSV vectored
  - Virus-like particles (VLP)
- Marburg
  - Recent NHP study at USAMRIID: 100% survival following challenge w/ lethal dose of MBGV and then post-exposure treatment w/ recombinant VSV-GP Marburg vaccine

Overview of VHFs

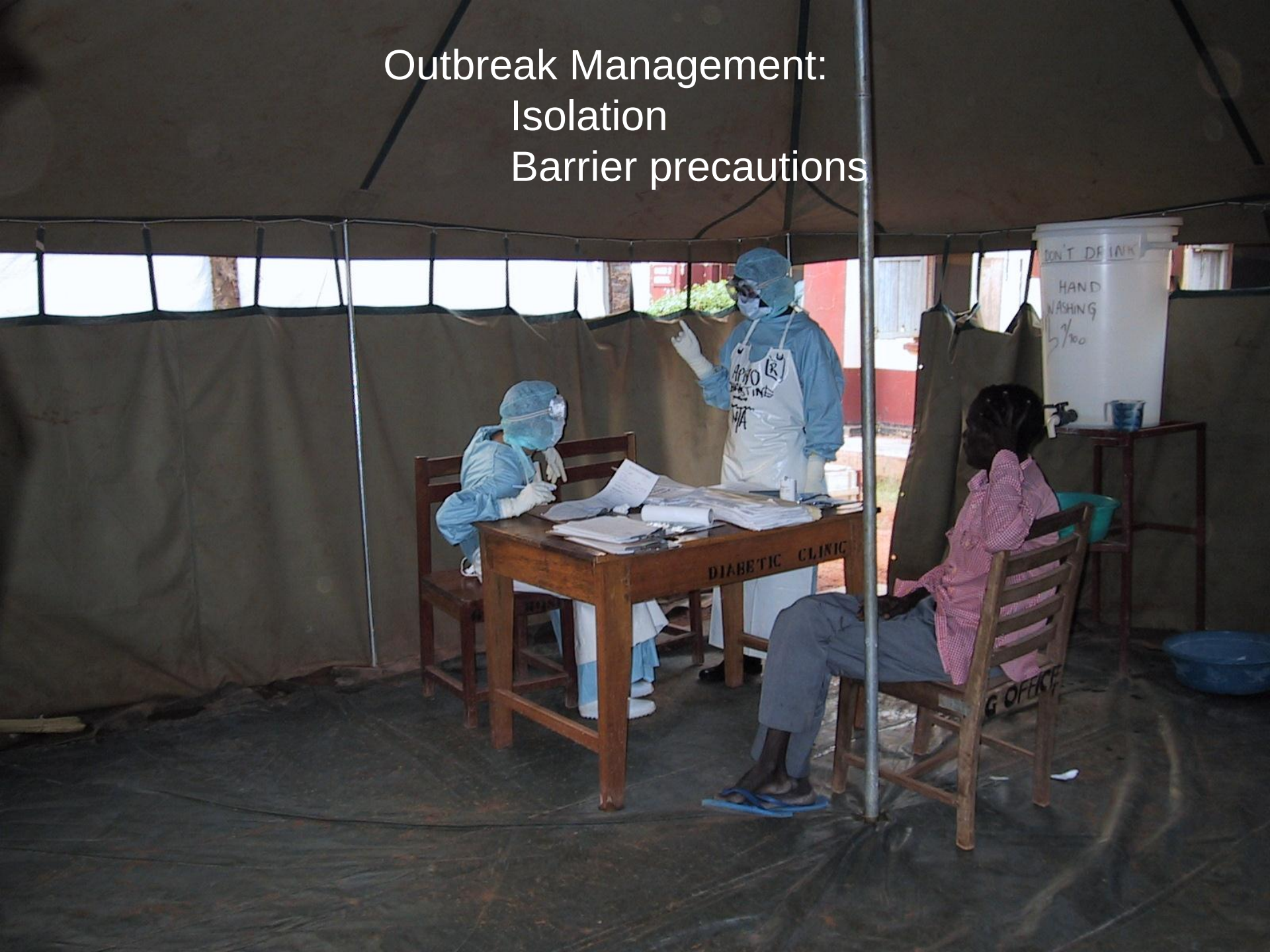
- **Prevention**
  - BACK TO THE INITIAL CASE PRESENTATION…
    - 18 HCPs identified as being **HIGH** risk exposures
    - Offered oral ribavirin post-exposure prophylaxis
    - 2 individuals had more significant symptoms to meds
    - Both were found to have developed antibodies to the CCHF virus

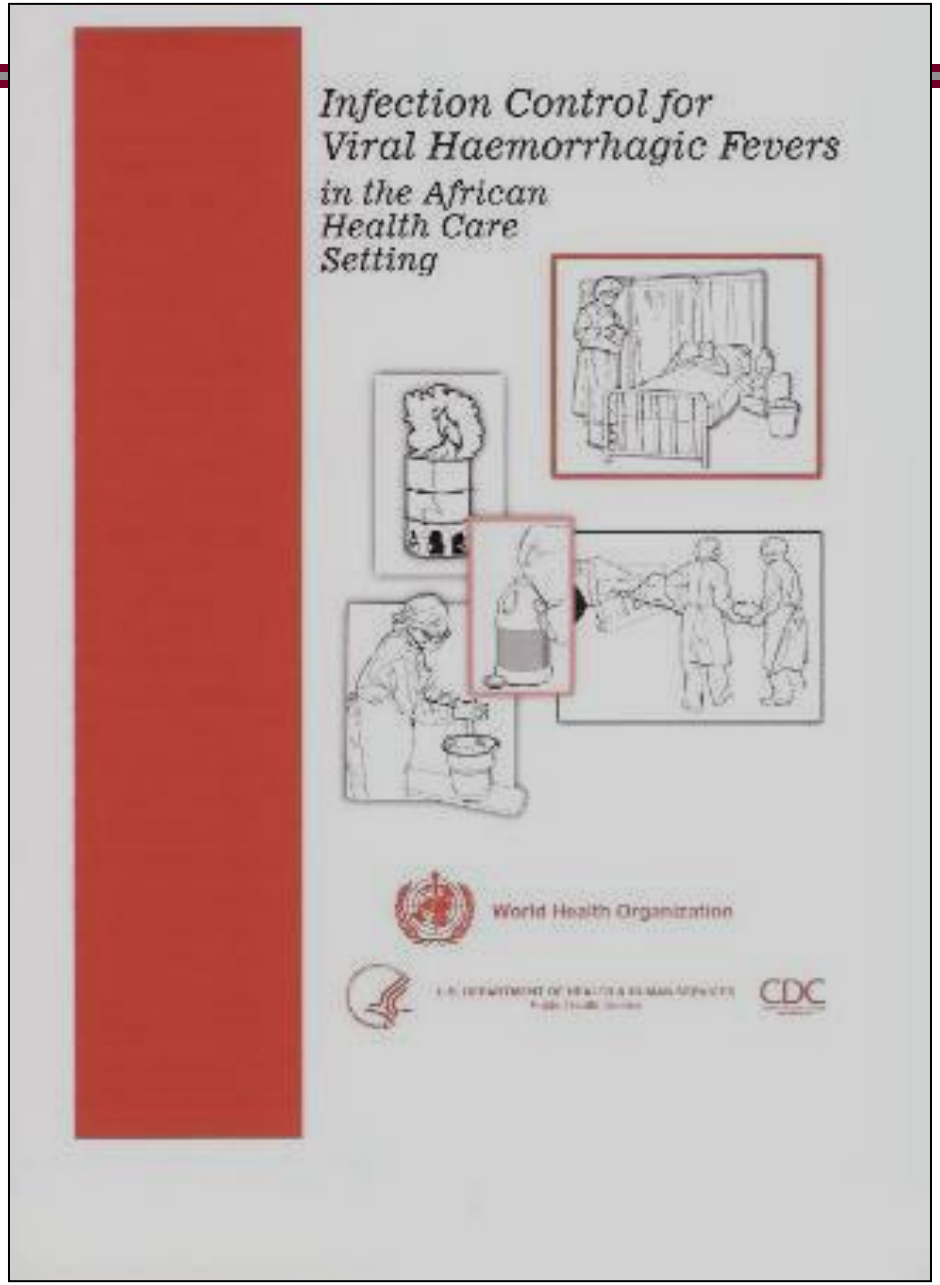
Overview of VHFs

- CDC Recommendations - when to go “hot”
  - Standard Precautions in initial assessments
  - Private room upon initial hospitalization
    - “Barrier precautions” – including face shields, surgical masks, eye protection **within 3 feet** of patient (double glove, impermeable gown)
    - Negative pressure room not required initially, but should be considered early to prevent later need for transfer
  - Airborne precautions if prominent cough, vomiting, diarrhea, hemorrhage
    - E.g. HEPA masks, negative pressure isolation

MMWR 1988;37(S-3):1-16. MMWR 1995;44(25):475-79.

Outbreak Management:
Isolation
Barrier precautions





www.cdc.gov/ncidod/dvrd/spb/mnpages/vhfmanual.htm

Overview of VHFs

- Identify a minimum level of Standard Precautions
  - Establish routine hand washing
  - Establish safe handling and disposal of used sharps
    - Minimize the use of sharps if possible
  - Be prepared to intensify Standard Precautions and include VHF isolation precautions
  - Identify a VHF coordinator to oversee and coordinate activities associated with VHF isolation precautions

Overview of VHFs

- Isolation Procedures
  - Isolate the patient in a pre-selected area
  - Wear protective clothing:
    - Scrub suit, gown, apron, two pairs of gloves, mask, headcover, eyewear, rubber boots
  - Clean/disinfect spills, waste, and reusable safety equipment, soiled linens, and laundry safely
  - Use safe disposal methods for non-reusable supplies and infectious waste
  - Counsel staff about the risk of transmission
  - Limit exposure to patient (use an “authorized” list and use a guard if necessary)
  - Provide information to families and the community about VHF prevention and care of patients

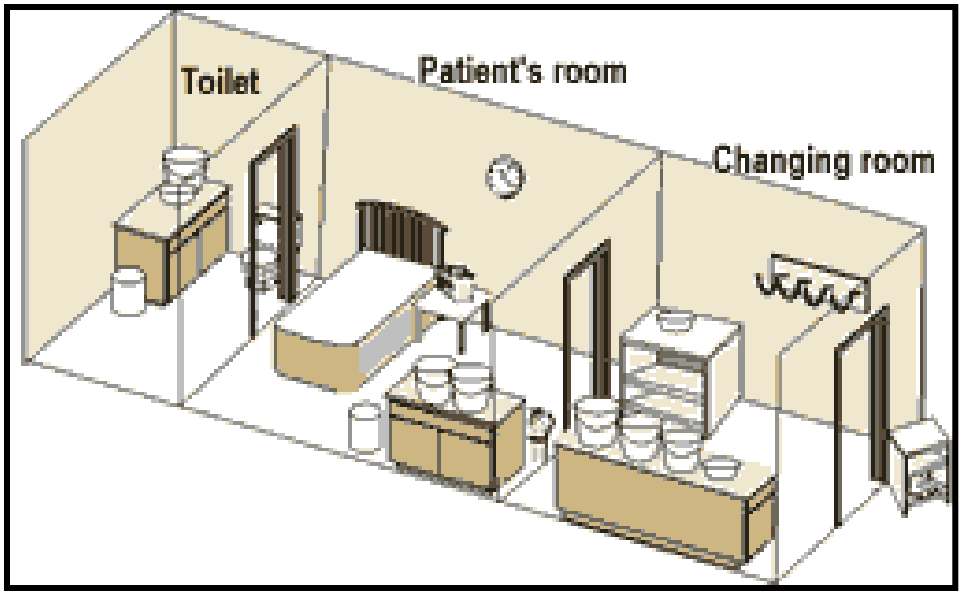
WHO VHF Africa Manual

Overview of VHFs

- Isolation Area
  - Single room with adjoining toilet or latrine
    - Prefer to use chemical toilets if possible (5% sodium hypochlorite)
    - Changing area to don PPE
    - Hand washing stations
  - Separate building or ward for VHF patients only
  - An area in a larger ward that is separate and far away from other patients
  - An uncrowded corner of a large room or hall
  - Any area that can be separated from the rest of the health facility

WHO VHF Africa Manual

Overview of VHFs



– Disinfection solutions
  - 0.5% sodium hypochlorite (Dakin's solution)
  - 2% glutaraldehyde
  - Phenolic disinfectants (0.5%-3.0%)
  - Soaps and detergents

WHO VHF Africa Manual

Overview of VHFs

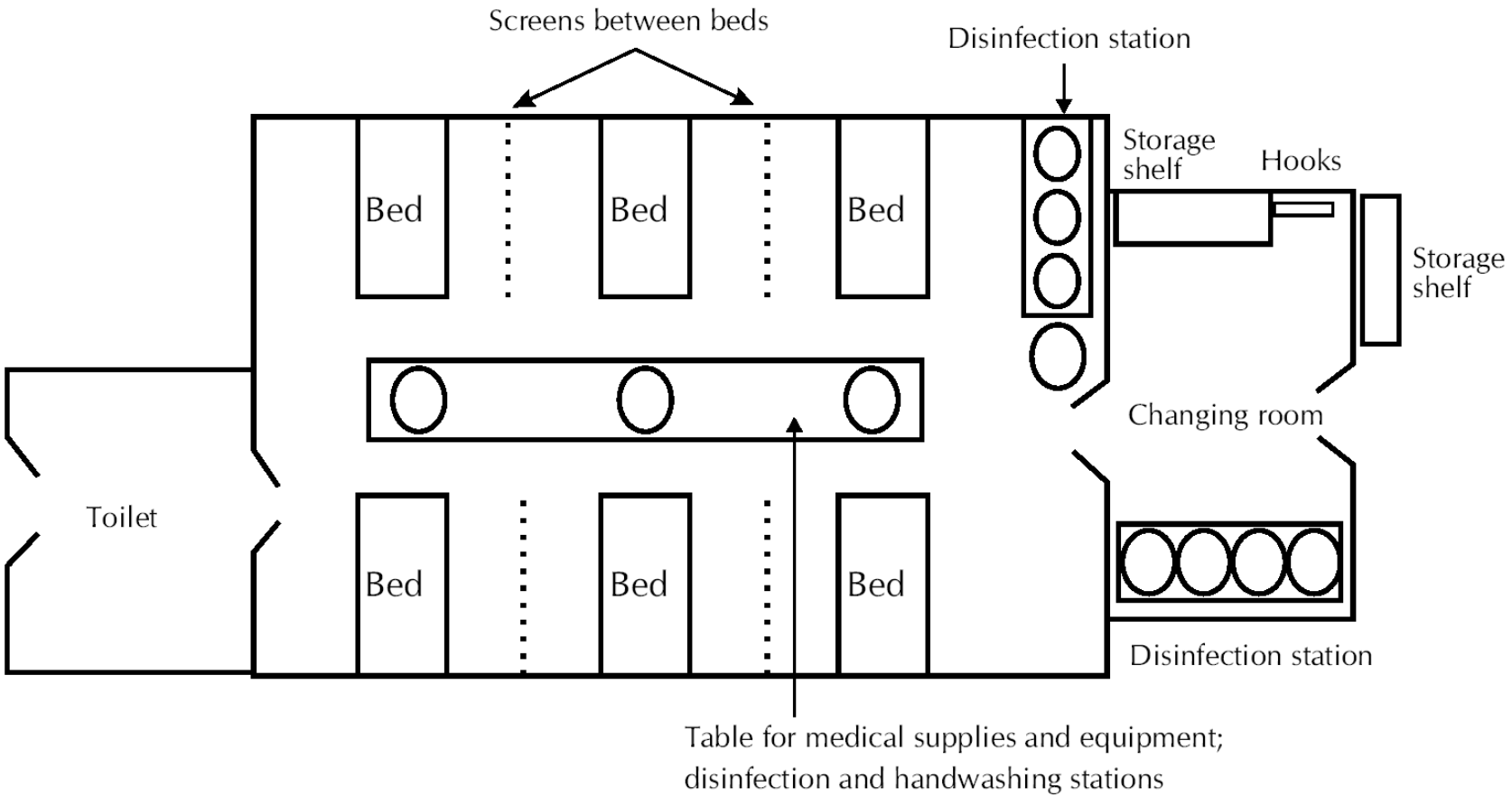


Fig. 10. A sample layout for several patients

Identify a single lab personnel that will handle the samples

Overview of VHFs

- First Aid for Exposures
  - Anticipate in advance – be prepared
  - Wash / irrigate wound or site immediately
  - Mucous membrane (eye, mouth, nose)
    - Continuous irrigation with rapidly flowing water or sterile saline for > 15 minutes
  - Percutaneous
    - Scrub for at least 15 minutes while copiously soaking the wound with soap or detergent solution
      - Fresh Dakin's solution (0.5% hypochlorite)

Overview of VHFs

- Casual contacts:
  - Remote contact (same airplane/hotel)
  - No surveillance indicated
- Close contacts:
  - Housemates, nursing personnel, shaking hands, hugging, handling lab specimens
  - Place under surveillance when diagnosis confirmed
  - Record temperatures twice daily x 3 wks
  - Notify for temperature >=101
- High-risk:
  - Mucous membrane contact (kissing, sex) or needle stick or other penetrating injury involving blood/body fluid
  - Place under surveillance as soon as diagnosis is considered
  - Immediately isolate for temperature >= 101

If you are dealing with something where ribavirin may be of benefit consider it as a post-exposure prophylaxis option

MMWR 1988;37:1-16

Ebola

Ebola

- Filovirus (Marburg virus is related)
- Several different strains
  - Zaire, Sudan, Ivory Coast, Bundibugyo, (Reston)

- First identified in 1976

- Has become the “prototypical” VHF
  - Classic bleeding diatheses
  - High case fatality rates
  - Significant nosocomial risk
  - Incubation typically 8 – 10 days (up to 3 weeks)

Ebola

- Current Outbreak
  - Affecting Sierra Leone and Liberia
    - No new cases in Guinea recently where it started in March
  - A record number of cases
    - Cases = 1048 (632 deaths; 60% CFR)
    - In the past week alone there are 67 new cases (19 deaths)
  - The current situation is far from stable

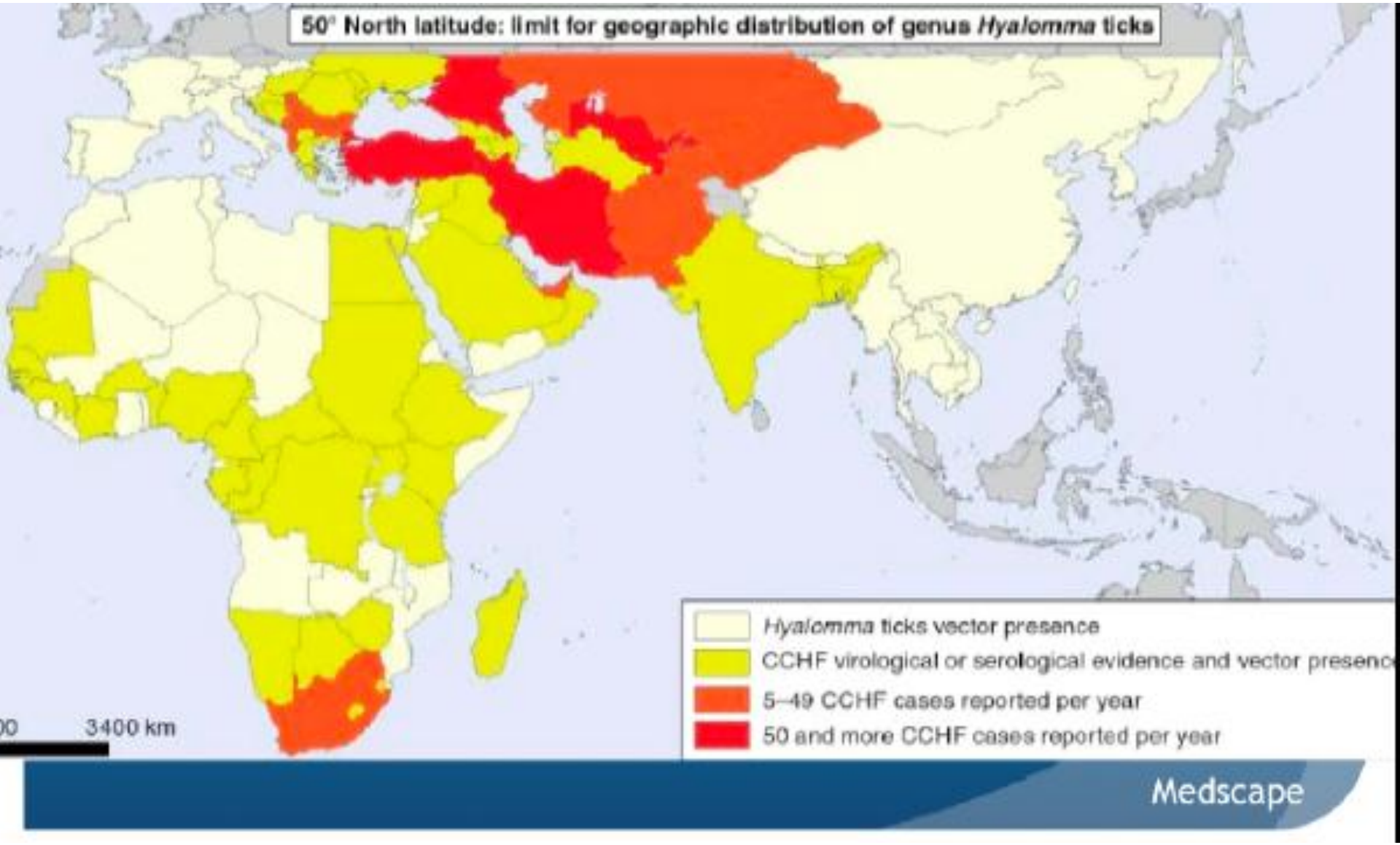
Ebola

- Treatment is primarily supportive
- In the works…
  - Recombinant human monoclonal antibodies against the envelope glycoprotein
  - Vaccine still in pre-clinical stage
    - DNA vaccines
    - Live viral vector vaccines
  - Medications:
    - Pyrazinecarboxamide derivative, T-705 (favipiravir)
    - Broad-spectrum nucleoside analogue (BCX4430)
    - Recombinant nematode anticoagulant protein (NAP)
      - inhibits activated factor VII-tissue factor complex

Crimean-Congo Hemorrhagic Fever

Crimean-Congo Hemorrhagic Fever

- Geographic regions
  - 12th Century: Tajikistan
    - HF syndrome: blood in urine, rectum, gums, vomit
  - 1944-45: First clinical description
    - Soviets (N=200, CFR = 10%) assisting peasants in Crimea
  - 1956: febrile patient in Belgian Congo
  - Common antigenic structure: Crimea & Congo viruses = CCHF


50° North latitude: limit for geographic distribution of genus *Hyalomma* ticks
Hyalomma ticks vector presence
CCHF virological or serological evidence and vector presence
5–49 CCHF cases reported per year
50 and more CCHF cases reported per year
3400 km
Medscape

CCHF

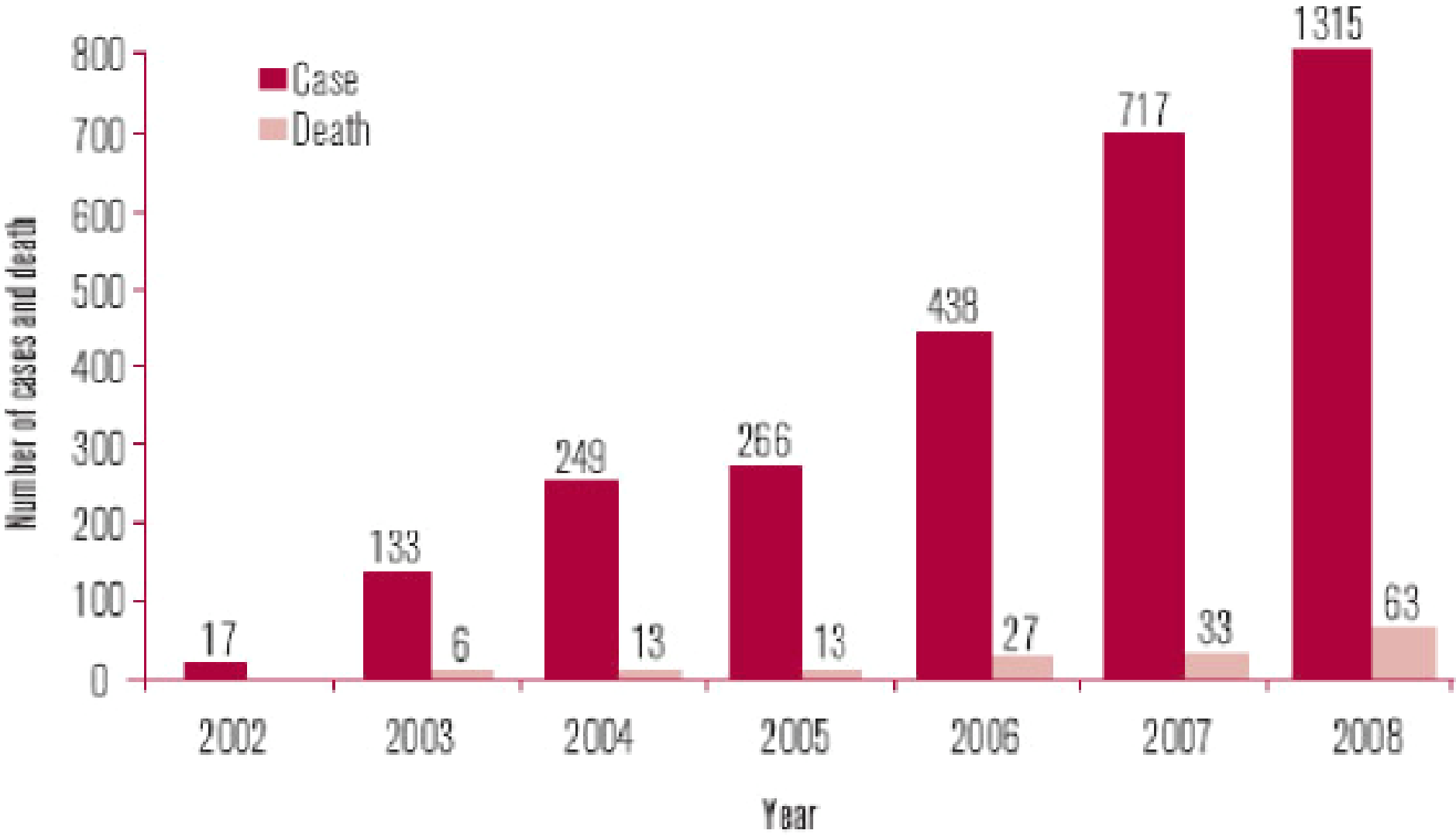
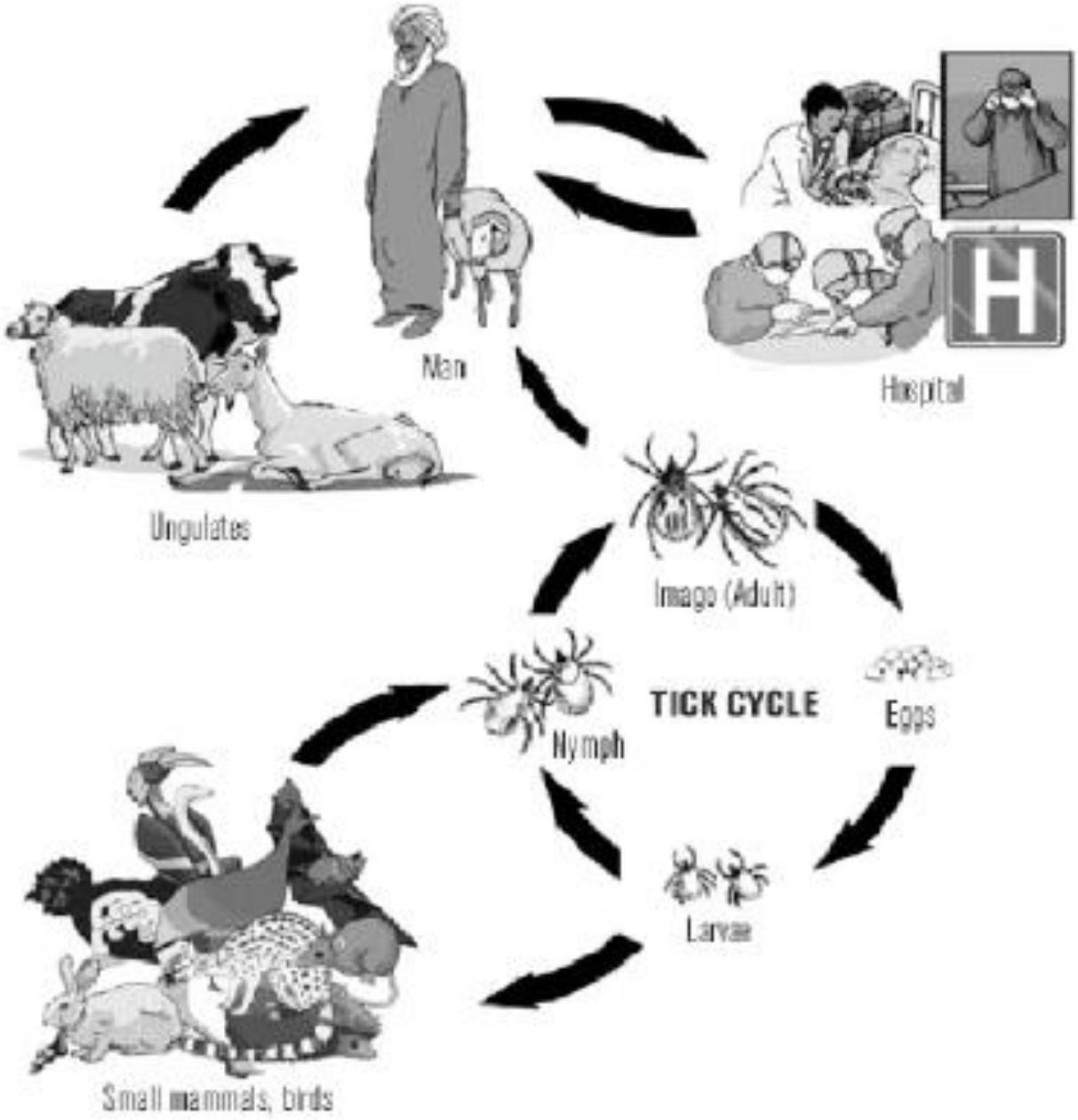


Figure 5. Number of Crieman-Congo hemorrhagic fever cases and deaths in Turkey between 2002-2008.[32]


Man
Hospital
H
Ungulates
Imago (Adult)
Eggs
TICK CYCLE
Nymph
Larvae
Small mammals, birds

Crimean-Congo Hemorrhagic Fever

- Exposure Risks
  - Ticks (*Hyalomma* sp.) – primary vector
    - Bite (increased exposure in Spring and Summer)
    - Crushed against skin
  - Animals
    - Rabbits, small mammals and birds – reservoir
    - Hoofed mammals (ungulates) – may be infected but won't show evidence of illness
    - Contact with dead animals (farmers, slaugherhouse, undercooked meat)
  - Nosocomial risk (many HCP have died)
- Mortality Rates: 3-70% (typically 20-30%)

Crimean-Congo Hemorrhagic Fever

- Diagnosis
  - ELISA (antigen capture as well as antibody)
  - RT-PCR (blood or tissue)
  - Virus isolation
  - Immunohistochemical staining
- Some predictors for severity in literature

Crimean-Congo Hemorrhagic Fever

- Containment & Prevention
  - Several reports in the literature indicating high risk of nosocomial transmission to HCPs
    - One report of a patient acquiring CCHF from being in same hospital room
  - Turkish study of HCPs in setting with high number of cases showed high rates of PPE use was associated with only a 0.53% seroprevalence rate
  - The 2 HCP who seroconverted in our initial case admitted to accidental mask slippage during care where aerosolization was a high risk

Int J Infect Dis. 2013 Nov;17(11):e1046-50
IntJ Infect Dis. 2009; 13: e105-7

Crimean-Congo Hemorrhagic Fever

- Containment & Prevention
  - Ribavirin
    - High risk contacts can be considered
    - Use oral ribavirin
      - The CCHF case from Afghanistan recommended 600 mg PO twice daily for 14 days (only took meds for 7 days in all cases)

Crimean-Congo Hemorrhagic Fever

- Treatment
  - Supportive Care
  - Ribavirin controversy
    - In-vitro activity against CCHF
    - No randomized controlled trials
    - Many case reports and case series indicating efficacy
    - Several others indicate no significant benefit
    - CDC does not “fully” recommend it’s use
    - WHO recommends its use for CCHF (as well as Lassa, Junin, and hantavirus with renal syndrome)
    - DoD has a phase 2 open label study for ribavirin treatment of Lassa and CCHF (clinicaltrials.gov - NCT00992693)

Crimean-Congo Hemorrhagic Fever

Table 1. Characteristics of SSI Parameters for Crimean-Congo Hemorrhagic Fever

SSI Parameter	Score
Platelet count, $\times 10^3$ platelets/mm^3	
>150	0
150–50	1
49–20	2
<20	3
aPTT, sec	
≤34	0
35–45	1
46–59	2
>60	3
Fibrinogen level, mg/dL	
≥180	0
179–160	1
159–120	2
<120	3
Bleeding	
No	0
Petechia	1
Ecchymosis	2
Bleeding	3
Somnolence	
No	0
Yes	1

Abbreviation: aPTT, activated partial thromboplastin time; SSI, severity scoring

- Severity Scoring Index
  - 0-2 = mild disease
  - 3-9 = moderate
  - 10-13 = severe
- Those with moderate disease had significantly better outcomes when receiving ribavirin
- Individuals with severe disease did better with corticosteroids added

CID 2013; 57:1270-4

Crimean-Congo Hemorrhagic Fever

- Treatment
  - Ribavirin appears to be beneficial to overall survival in at least moderate to severe disease
  - Earlier the therapy the better (within first 4 days of illness)
  - Corticosteroids in severe illness in addition to ribavirin may be beneficial to survival

Lassa

Lassa

- Geographic regions
  - *Arenavirus* first described in Nigeria in 1969 with distribution primarily in West Africa
  - Outbreaks have occurred in:
    - Central African Republic
    - Guinea
    - Liberia
    - Nigeria
    - Sierra Leone (1987)
      - 10-16% of all adult medical admissions
        30% of adult deaths
      - 25% of all maternal deaths
  - Serological evidence found in Democratic Republic of the Congo, Mali, and Senegal

Lassa


Outbreaks of Lassa Fever
Serological evidence of human infection
Mali
Senegal
Guinea
Nigeria
Sierra Leone
Liberia
Central African Republic
Congo
Atlantic Ocean
N
0 km 800

Lassa

- Exposure Risks
  - Reservoir: *Mastomys* rodents
    - Rodent-to-human:
      - Inhalation of aerosolized virus from rodent urine and feces
      - Ingestion of food or materials contaminated by infected excreta
      - Catching and preparing *Mastomys* as a food source
  - Human-to-human:
    - Direct contact with blood, tissues, secretions or excretions
    - Needle stick or cut
    - Inhalation of aerosolized virus suspected
  - Mortality Rates: 15-20% of hospitalized

Lassa

- Exposure Risks
  - Nosocomial Outbreaks
    - Dry season (JAN to APR)
    - All age groups and both sexes
  - Pregnant women and fetus at high risk
  - The Kenema Government Hospital
    - January to April 2004
    - 95 pediatric cases admitted
    - 50% of all cases aged under 15 years
      - CFR was 30–50% in children <5
      - CFR was 71% in children <1

Dr. Conteh attempted femoral venipuncture and sustained a needlestick.

(WHO, Weekly Epi Record, MAR 2005)

Lassa

- Diagnosis
  - Clinical diagnosis is tough
    - May present with nonspecific symptoms
    - Hemorrhagic manifestations may not be evident
    - Neurologic symptoms (**hearing loss**, tremors, encephalitis)
  - ELISA (antibody or antigen)
  - Viral culture (wouldn't do this unless you have BSL-4)
  - Immunohistochemical staining of tissue
  - RT-PCR

Lassa

- Containment & Prevention
  - Rodent control (food storage is key)
  - Use of VHF barrier precautions can limit or eliminate healthcare worker risks
  - Isolation of patients as discussed
  - Lassa vaccine
    - USAMRIID had a vaccine based on a live viral platform that protected monkeys against a lethal challenge of Lassa
    - Monkeys did not have symptoms, BUT were found to have circulating virus

PLoS Med 2005; 2(6): e183

Lassa

- Containment & Prevention
  - Ribavirin
    - High risk contacts can be considered
      - Needle sticks or sharp injury
      - Mucous membrane or broken skin with blood/secretions
      - Participation in emergency procedures without PPE
      - Prolonged contact in enclosed space (e.g. med evac)
    - Use oral ribavirin
      - 800 mg daily for 10 days (EID article)
      - 35 mg/kg x 1 (up to 2.5 g) then 15 mg/kg (up to 1 g) TID x 10 d

CID 2010; 15;51(12):1435-41
EID 2010; 16 (20): 2009-2011

Lassa

- Treatment
  - Supportive Care
  - Ribavirin
    - If used early (within 6 days) may significantly reduce mortality (76% to 9%)
      - If you wait to start ribavirin after 6 days, rate goes up to 47%
    - WHO recommends use (CDC also promotes its use)
    - DoD use via the open label study (see CCHF info above)

N Engl J Med 1986; 314:20–6.
Antiviral Res. 1994;23:23
Rev Infect Dis. 1989;11:S750

Hantaviruses

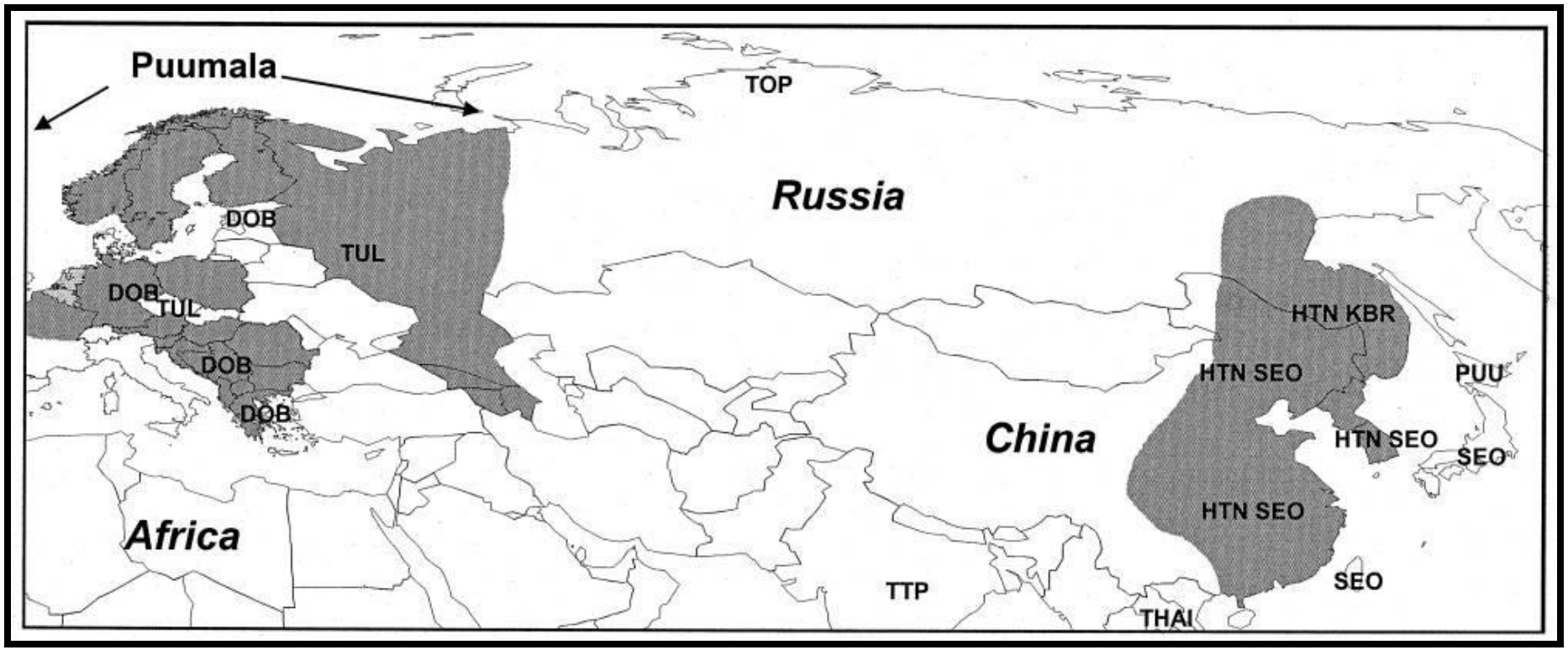
Hantaviruses

- History
  - 1934: First published case of HFRS
  - 1951-1953
    - United Nation's troops in Korean War (near Hantaan River)
    - 3000 cases of fever + hemorrhage in 33%
  - 1978: virus isolated
  - 1986: US – Korean military joint field exercise
    - 14 cases of HFRS among 3,754 US Marines
    - 10 were hospitalized & 2 died (CFR = 14%)
    - Cases confirmed by serologic testing

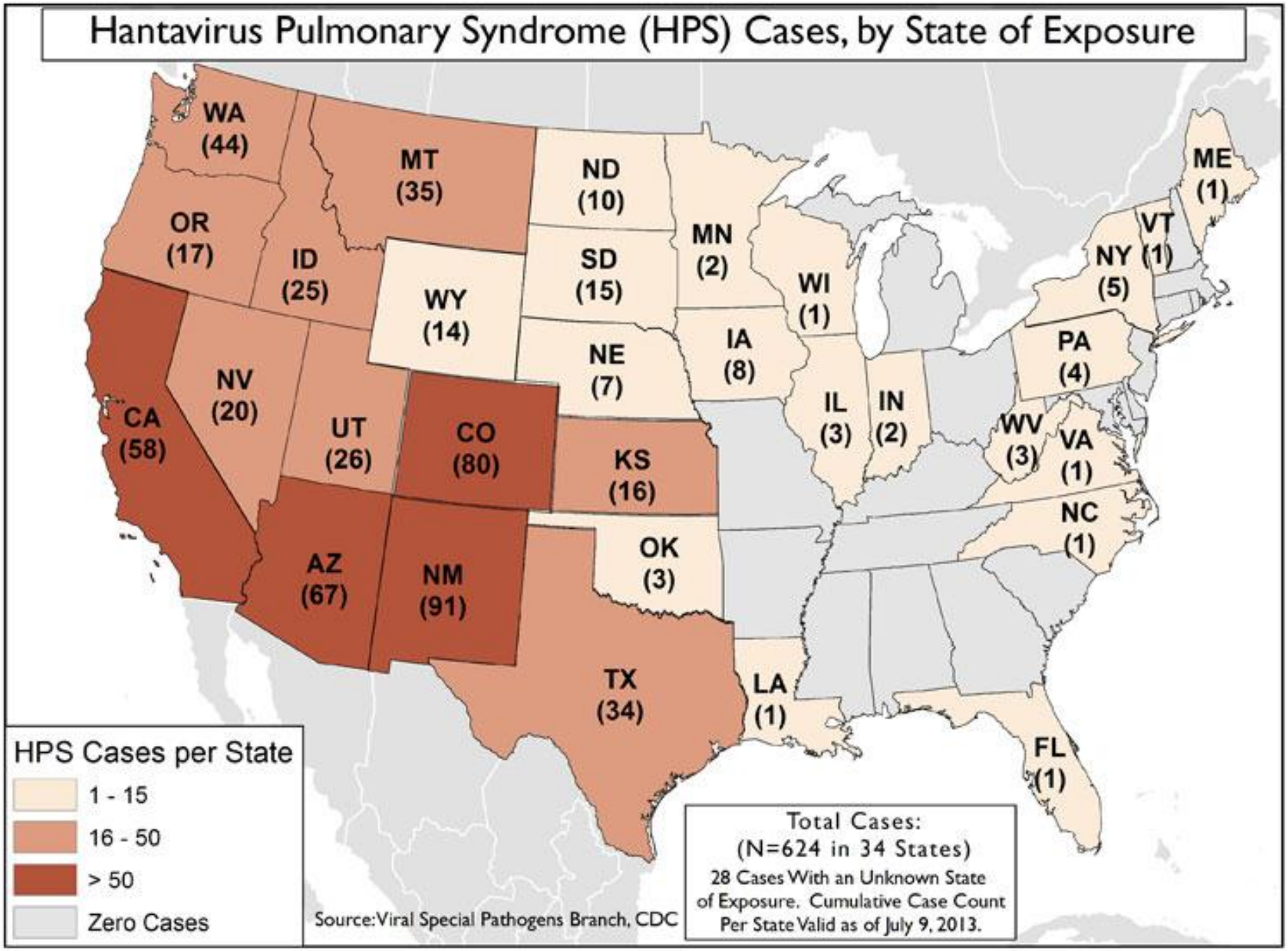
MMWR Feb 19, 1988/37(6);87-90,95-6

Hantaviruses

- Geographic regions
  - "Old World":
    - Hantaan (Korea, China, Eastern Russia)
    - Dobrava (Balkans)
    - Seoul (Asia)
    - Puumala (Scandinavia, Western Russia, Europe)
  - "New World": Sin Nombre (U.S.), Andes



Field's Virology, 4th Ed. Chapter


Hantavirus Pulmonary Syndrome (HPS) Cases, by State of Exposure
WA (44)
OR (17)
CA (58)
ID (25)
NV (20)
MT (35)
WY (14)
UT (26)
AZ (67)
CO (80)
NM (91)
ND (10)
SD (15)
NE (7)
KS (16)
OK (3)
TX (34)
MN (2)
IA (8)
MO
AR
LA (1)
WI (1)
IL (3)
IN (2)
MI
OH
KY
TN
MS
AL
GA
FL (1)
SC
NC (1)
VA (1)
WV (3)
PA (4)
NY (5)
VT (1)
ME (1)
HPS Cases per State
1 - 15
16 - 50
> 50
Zero Cases
Source: Viral Special Pathogens Branch, CDC
Total Cases:
(N=624 in 34 States)
28 Cases With an Unknown State of Exposure. Cumulative Case Count Per State Valid as of July 9, 2013.

Hantaviruses

- Exposure risks
  - Rodent excreta (aerosolized)
  - Reservoir
    - *Apodemus agrarius* : striped field mouse (Hantaan)
    - *Aedes flavicollis* : yellow necked mouse (Dobrava)
    - *Clethrionomys glareolus* : bank voles (Puumala)
    - *Rattus norvegicus* : rat (Seoul)
  - Demographic
    - Farmers, forest workers, soldiers in the field
    - Opening and utilizing previously unused buildings
    - 20 to 50 years in age
    - Male > Female
  - Human to Human (very rare, with Andes virus)

Hantaviruses

- Diagnosis
  - Presentation:
    - Hemorrhagic Fever with Renal Syndrome (Old World)
      - Incubation period may be 2-4 weeks
      - Flu-like symptoms, flushing or rash, red eyes, hemorrhagic symptoms possible
      - Acute renal failure
        - »Puumala may have a milder presentation
    - Hantavirus Pulmonary Syndrome (New World)
      - Early = nonspecific, flu-like symptoms
      - Late = severe shortness of breath and cough secondary to pulmonary edema
  - Lab diagnosis similar to other VHFs mentioned

Hantaviruses

- Containment & Prevention
  - Rodent control and maintain adequate food storage
  - Person-to-person transmission has only been identified with the Andes virus (causes HPS)
  - Vaccines are being developed
    - Recently completed a phase 1 study at WRAIR

Hantaviruses

- Treatment
  - Supportive care
  - Dialysis frequently required for “Old World”
  - Ribavirin appears to be of benefit in “Old World” cases, by decreasing mortality and improving renal morbidity
    - A double-blind, RCT of ribavirin in New World HPS did not indicate effectiveness

JID 1991;164(6):1119-27
Antiviral Res. 2009 Jan;81(1):68-76
CID 2004; 39 (9): 1307-1313.

Emerging Threats

"There are known knowns; there are things we know that we know.

There are known unknowns; that is to say, there are things that we now know we don't know.

But there are also unknown unknowns – there are things we do not know we don't know."

DONALD RUMSFELD
United States Secretary of Defense
February 12, 2002

Be on alert for emerging infections…

- Lujo hemorrhagic fever (Zambia, South Africa)
  - 4 out of 5 patients died
  - The lone survivor received ribavirin

EID 2009; 15(10): 1598-1602

- Alkhurma hemorrhagic fever (Saudi Arabi, Egypt)
  - Case fatality rate ~30%
  - Considered to be tick born
  - Hemorrhagic fever +/- encephalitis (similar to Kyasanur Forest Disease)

- Novel bunyaviruses (likely tick borne)
  - Severe Fever with Thrombocytopenia Syndrome virus (China)
  - Heartland virus (2 cases, no deaths; found in Missouri)

Emerging Threats

- Chapare Virus
  - Small cluster of cases occurred in rural Bolivia (2003-2004)
  - Hemorrhagic fever symptoms
  - Novel arenavirus found in 1 pt
    - 22 yo male, died on DOI 14

PLoS Pathog 2008; 4(4): 1-6

Summary

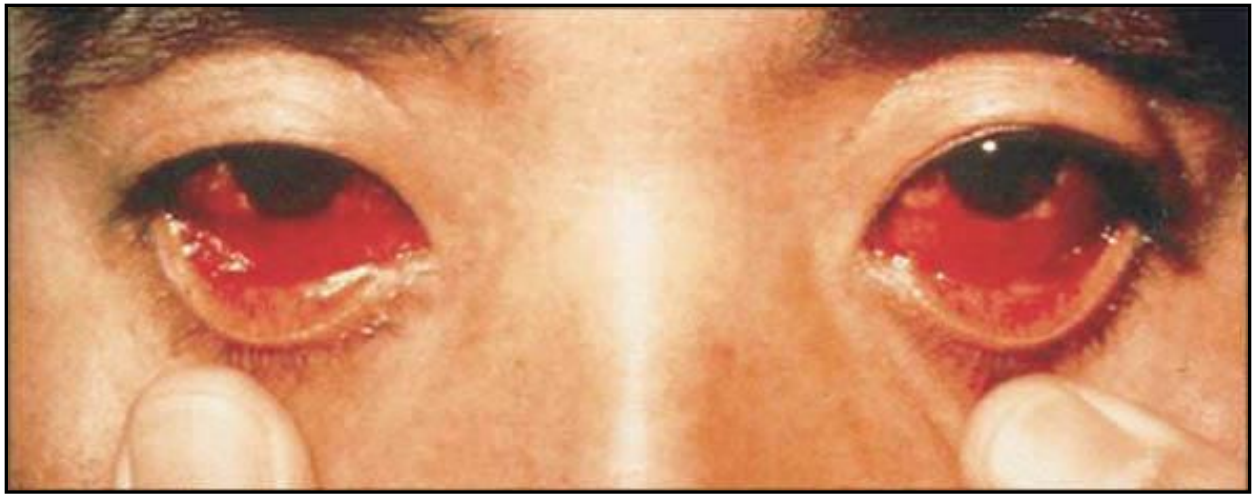
- VHF will start as flu-like illness and progress to organ failure (**bleeding may not be evident**)
- Have high concern for the nosocomial risk as the treating provider
- Masks, gloves, gowns, and eye protection at a minimum
- Have isolation plan, post-exposure plan, and evac plans ready
- Ribavirin may be of benefit to some (not all VHFs) if given **early**

Summary

- Ribavirin is an investigational drug for VHF, thus you need to use it on a research protocol
- Avoid rodents
- If you are in a remote tropical locale with little epidemiologic data, and there are cases of something that appears hemorrhagic in nature, consider the unknown

Final Thoughts

- Any fever in a traveler to a malaria endemic region is malaria until proven otherwise



- Any traveler with fever **AND** bleeding out of their eyeballs is VHF until proven otherwise

Questions?